an awareness that the pathway of discovery to translational research to clinical impact is bi-directional. We're picking up far more disease-associated changes in patients that we can take back to genetically tractable models to understand causal relationship and, ultimately, therapeutic or diagnostic utility.

So is the age of discovery over? Not by any measure. The primary reason we don't have frequent breakthroughs leading to cures is because of the limits of current understanding. A lot of what we do think we know is either over-simplified or incomplete. A major challenge for a world which is impatient and has huge expectations for economic and health pay-offs and "return on investment" is how to balance our clear need for new knowledge with the need of our society to improve quality of life. This is exacerbated by the impending demographic pressures of aging populations and spiraling healthcare costs. But the quality of translational research is entirely dependent on the quality of the discoveries being translated and it is clear that the most important predictor of future impact/utility/value of research is excellence. We must be careful to balance, for example, assessment of "commercial potential" in relation to scientific merit when making decisions of research funding. We need to better explain our work to both the public and to decision-makers. I'm optimistic that scientists want to get involved as demonstrated by our campaign that questioned the wisdom of vetting financial parameters before assessing scientific merit (www.sciencefunding.ca) which attracted over 1300 signatures. If we are to achieve a golden age for research, we each have the responsibility to explain and defend the scientific process that has provided so much knowledge and value to society to date.

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Essay

The unsolved mystery of vision

Richard H. Masland[1] and Paul R. Martin[2,3]

Vision looms large in neuroscience — it is the subject of a gigantic literature and four Nobel prizes — but there is a growing realization that there are problems with the textbook explanation of how mammalian vision works. Here we will summarize the evidence behind this disquiet. In effect, we shall present a portrait of a field that is 'stuck'. Our initial focus, because it is our area of expertise, is on evidence that the early steps of mammalian vision are more diverse and more interesting than is usually imagined, so that our understanding of the later stages is in trouble right from the start. But we will also summarize problems, raised by others, with the later stages themselves.

The standard visual system

In the view repeated in every textbook, visual coding proceeds in three stages. First, light is sensed by the retina and translated into neuro-electric signals. Here, in addition, the contrast and brightness of the signal are normalized: just as an automatic camera adjusts its own exposure, the retina maneuvers the intensities and contrasts of the natural world into a manageable operating range.

Second, the retina divides the raw visual signal — essentially a bitmap of the image — into parallel informational streams, each encoding a particular aspect of the visual input. These are reflected in the response to light of individual retinal ganglion cells, the neurons whose axons bundle together to form the optic nerve (Figure 1). In the standard model, two main types of ganglion cell feed the cortical pathways for conscious visual perception. One is represented by a set of cells which, because they are numerous, offer the brain a high spatial resolution and are responsive to standing contrast. For historical reasons these are usually called PC cells, because their signals pass through the parvocellular (PC) layers of the lateral geniculate nucleus (LGN) before reaching the visual cortex. A second set of cells — MC cells, whose signals pass through the magnocellular layers of the LGN — are fewer but have an enhanced sensitivity to images that flash or move. Both these cell types have 'concentric center–surround' organization: a supposedly general-purpose transmission strategy for encoding visual stimuli. For both these types of cell, the best stimulus is small and more or less circular, and the more intense the contrast of the stimulus, the more vigorous is the response of the cell.

What does the brain do with these signals? In the standard view, the real business of visual processing begins in the primary (striate) visual cortex. In the striate cortex a major recoding occurs, with the dramatic consequence that many of the cells become sensitive not only to a particular patch on the retinal surface, but to oriented line segments — to edges rather than to spots of light. More complex tunings also exist, in which the cortical cell responds to an edge regardless of the edge's location in space. This 'complex' transformation was initially conceptualized as a second step of abstraction, in which the cortex's detection of oriented edges was extended to the more general case (edge sensitivity freed of its association with a particular location in space). In summary, then: first, the retina transmits simple signals to the cerebral cortex; second, the cortex combines these simple signals to detect edges; and third, these fundamental building blocks are used to delineate the borders of objects and create visual perceptions.

Though probably intended by no one, this view has morphed into

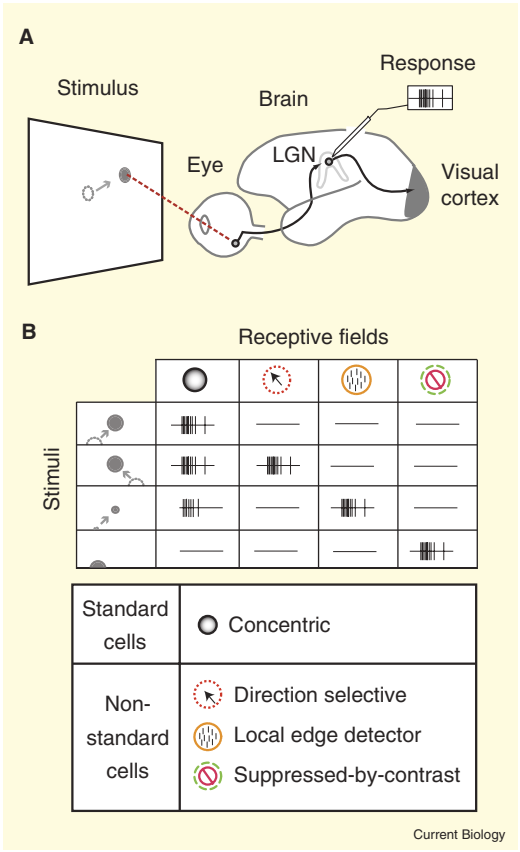

Figure 1. Measurement of receptive field properties.

(A) The response of a neuron (trains of action potentials or 'spikes') is monitored by extracellular recording in the subcortical visual system of an anaesthetized animal. Stimuli are introduced into the relevant part of the visual field so the selectivity of the neuron can be assessed. (B) Schematic tabulation of response selectivity. Each column shows the response of one cell type. Each row shows responses to one stimulus type. For example, the direction selective cell (second column) only responds when a stimulus moves through the receptive field from lower left to upper right. The cells that have standard concentric receptive fields are relatively unselective for the size and movement direction of the stimulus. The non-standard cell types show a much greater degree of selectivity.

a piece of fundamental dogma. Edge detection has come to be treated as though it is the only way in which mammalian vision can be achieved — as somehow defining evolution's ideal solution to the problem of representing images efficiently. Here we shall question that view. In the end, uncomfortable questions about the nature of vision will be raised. We are not the first to raise such questions, nor will we offer a simple solution. The attempt here is to bring the questions into focus, by assembling reasons for doubting that the current framework for thinking about vision is secure. We begin by summarizing three difficulties.

All mammalian retinas send non-standard signals to the brain

Careful exploration of the primate subcortical pathway has now confirmed beyond doubt that, just as in other mammalian species, the functional input to the primate cortex consists of multiple, parallel arrays (Figure 2) [1–4]. Some of these inputs even bypass the major route through the striate visual cortex to feed directly to higher-order cortical areas [5]. Much of this had been shown in classic studies of both cat and monkey [6–10] but the information was not used by the pioneers of cortical exploration. An aggressive slice of Occam's razor was required to make sense of the properties of cortical neurons; it consisted of assuming that standard concentric receptive fields form the sole input stage [11]. Furthermore, in the retinas of primates, the non-standard cells are low in relative numbers. What this means for visual processing will be discussed shortly; in practical terms it means that an electrode randomly inserted into the afferent visual pathway will almost certainly strike the receptive field of a concentric cell. Because non-standard cells are infrequent, most experimenters have naturally armed themselves with stimulating apparatus best suited to studying the concentric cells, making non-standard cells the 'outliers'.

The second issue is illustrated in Figure 3. The upper graph of the figure shows the responses of a concentric cell type (a PC cell). The basic pattern of response is very familiar to visual neuroscientists: PC cells show a band-pass response to spatial frequency — the maximum response is caused when the width of a bar of the grating exactly matches the center of the cell's receptive field. But now consider the responses of a non-standard cell recorded in the same LGN within hours of the PC cell (Figure 3B). This time the location of the cell is the so-called koniocellular or KC pathway, a loose collection of non-standard cell types that is customarily summed up, if it is mentioned at all, as the 'blue color pathway'. This cell shows a 'suppressed-by-contrast' receptive field [6,7,12,13]. The response is almost a complete inverse of the pattern shown by the (standard concentric) PC cell. For the range of spatial frequencies that excite the PC cells, the suppressed-by-contrast cell is quiescent, because these cells show monotonic *decrease* in response with increasing contrast. These cells have quantitatively similar properties in cats and monkeys [12,13]. We can only speculate what such suppressed-by-contrast coding could contribute to cortical processing — might they act to 'mask out' regions of uniformity such as a cloudless sky? — because such responses do not yet have a place in the standard model of mammalian vision.

Non-primate mammals see well using non-standard cells

For primates, a defender of the standard model can take refuge in the fact that the non-standard cells are relatively infrequent. But this is not true for the retinas of cats, rabbits, rats and mice [7,8,14–16]. Furthermore, in absolute numbers (~100,000) the number of non-standard cells in the primate retina is close to the total number of cells in the retina of the rat or cat [17]. The acuity of vision in cats, rabbits,

rats and mice is lower than that of primates, but acuity isn't everything. The visual systems of all these creatures provide a perfectly useful way to interact with the visual world. Anyone who doubts this is invited to try to sneak up on a rabbit in the field, or to catch a mouse without using a mousetrap (a straightforward task for the average domestic cat).

It is understandable, if only because of medical motivations, for humans to concentrate on the primate retina. By concentrating on primate vision, though, the attempt to understand seeing is rendered susceptible to experimenter-centered introspection. The dense packing of a primate's retinal ganglion cells is fine for spotting edible fruits on a distant tree, or for reading the New York Times, but there is little reason to consider tasks like these as the *summum bonum* of vision. In the overall evolutionary picture this extreme of visual acuity can just as well be considered a niche-specific adaptation, for long-distance detection of high contrast objects. Most mammals do not have a fovea — the specialized region for high-acuity found in primate retina — but vision without a million densely packed ganglion cells remains quite workable. This is illustrated in Figure 4, which demonstrates that humans are readily capable of visually driven cognition in the absence of high acuity vision [18].

Among non-primate mammals, the coding of visual stimuli has been particularly well-studied in the rabbit [19–23]. Rabbits have large eyes, with optics better than those of many primate species. Their retinas do contain the standard concentric types of ganglion cell, in the rabbit termed 'brisk-transient' and 'brisk-sustained' cells. However, these standard cells make up less than one quarter of all the retinal ganglion cells, which are distributed among ~12 anatomical and functional types [14,21]. It is now clear that each of these 12 types is tuned to a distinct feature of the visual input, along the lines shown in Figure 1. The importance of this fact is that the rabbit's brain must receive a preponderance of non-standard visual signals. This information is not new: what is new is the evidence that most or all mammalian retinas transmit a diversity of visual codings to the brain [4,13,24,25], and that this diversity should be incorporated into any realistic view of how vision works.

A famous case in point is the directionally selective neuron, which reports to the brain which direction a stimulus is moving. One type of directionally selective cell projects directly to a brainstem nucleus concerned with eye movements [26]. But it is not commonly recognized that there is a *second* type of directionally selective cell (the On-Off type) that projects not only to the midbrain but also through the lateral geniculate body to the visual cortex [19]. These are not rare neurons, yet there is no room for such information in the textbook view of how the mammalian visual system works. These signals undoubtedly reach the visual cortex, but what do they contribute?

A second non-standard cell type (identified thus far in rabbits, cats, and mice) is the so-called local edge detector. Like the directionally selective cells, these were also once thought to be rare cells, but we now know that this was because of electrode sampling error: they probably comprise ~15% of all ganglion cells [23]. Signals from these cells, too, reach the visual cortex, but

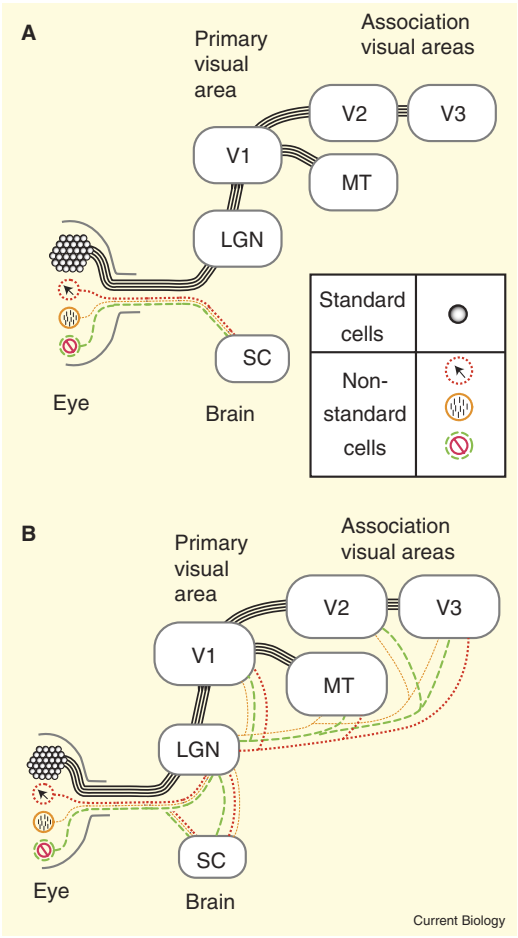

Figure 2. Views of the visual system.

(A) The textbook view of the primate visual system. This view takes the brain of the macaque monkey as the paradigmatic case. The retina is shown as populated by a large number of retinal ganglion cells — the neurons whose axons form the optic nerve — of a simple and basic type; these are often termed 'concentric cells' because they respond to a stimulation that falls within a circular region of the retina, with a concentric zone where light inhibits them. The retina also contains a small number of retinal ganglion cells that respond to light in other ways, but these are traditionally assumed to project only to vegetative centers of the midbrain. The superior colliculus (SC) is one such center. The concentric cells project to a relay nucleus in the thalamus, the lateral geniculate nucleus (LGN), which in turn relays the signals to the primary visual cortex (V1). After entering the primary visual cortex, the signals are transformed by 'association' cortical areas (named V2, V3, MT, and others not shown). (B) A more realistic view of the primate visual system. Some of the non-standard ganglion cells project directly to the LGN, and thence to the primary visual cortex. In addition, the superior colliculus is not a dead-end pathway: it projects to the LGN and other thalamic centers, so that information from the non-standard codings can re-enter the primary visual pathways. Finally, none of the pathways are one-way. The most dramatic case is the pathway from LGN to visual cortex, where the reciprocal pathway is in fact larger than the feed-forward path; but reciprocal projections occur among all of the visual centers.

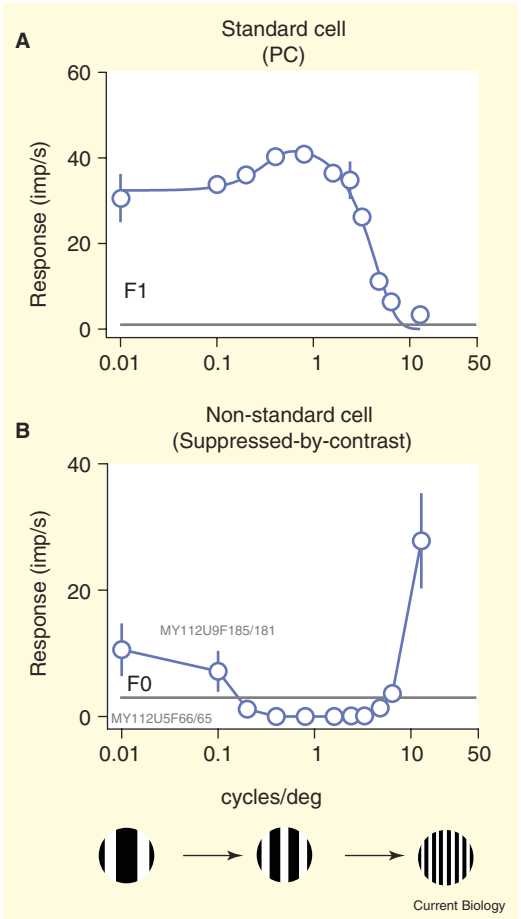

Figure 3. Comparison of a standard and a non-standard receptive field.
The cells were stimulated by a drifting grating of variable spatial frequency (frequency here is expressed as grating cycles per degree of visual angle). The standard concentric cell (A) behaves as expected: when the width of a grating cycle is close to the width of the receptive field center, the cell is strongly driven. The suppressed-by contrast cell (B) seems to have no such optimum: instead of excitation, the cell is silenced when the grating is present, and this remains true even at a wide range of bar widths.

their responses lie far outside the envelope of the standard visual responses [8,22,23]. These cells respond best to small, slowly moving targets such as a predator or prey animal moving at a distance. However, if there are many small objects, as in a textured field, the cells are almost perfectly unresponsive. In other words, the cells respond to a small moving object, but only when it is present in isolation.

The local edge detectors appear to be the most numerous type of retinal ganglion cell in the rabbit, but they have not been included in the standard view of the visual system. Could these cells form a system for long-range movement analysis? How does the visual cortex process the signals from these cells? How many other mammalian species sample the world with both the standard brisk sustained cell, and also the local edge detector — or even with codings that remain to be discovered?

The visual cortex is smarter than textbooks admit

Even if we were to assume that the inputs to the cortex contain only standard receptive fields, it is now clear that processing in the visual cortex does not proceed along the originally envisioned path of simple, complex, and hypercomplex or 'end stopped' cells. These issues have been thoughtfully discussed in the specialised literature [27–30]. The problems start with the obvious fact that nearly all cortical neurons are intractably non-linear, which calls into question the utility of hierarchical schemes with linear assumptions at their core [31,32]. Second, the idea of three main cell types — simple, complex, and hypercomplex — is a gross mismatch with the rich diversity of cortical cell types revealed by anatomical methods [33,34]. Third, the cortical neurons depend not only on afferent signals from the thalamus, but also on a variety of contextual signals, such that objects and events throughout the visual field can change the selectivity of cortical neurons [27,35]. The responses of cortical neurons are not even fixed in time: ablating a region of the retinal surface, which causes a local blind spot, creates responses in the cortical neurons that represent the neighboring regions of visual space [36].

None of this should be surprising in light of the cortical anatomy. Only ~10% of the input an individual cortical neuron comes from thalamic afferents [37]: the rest comes from local intracortical neurons or from neurons located in distant parts of the cerebrum, where the visual cells have acquired unknown tricks, and send unknown messages back to the neurons of the primary visual area.

In summary, it seems clear to us and to others that the standard view of visual system function is in trouble from stem to stern. What steps would get things moving again?

Step I: Rebuild the foundation

Recent good news is that our ability to visualize retinal neurons has over the last 5 years undergone an unnoticed revolution, such that it is now easy to image neurons in large numbers, with unprecedented clarity. Their contacts and stratification are readily resolved and they can be classified not only 'by eye' but using objective classification methods [15,16]. The relevance here is that morphological types are associated in a one-to-one relationship with physiological types (reviewed in [24]). Thus, the structural classes of retinal neuron specify the number of parallel functional encodings that are reported to the brain.

In all mammalian visual systems thus far studied, anatomical evidence indicates that the number of afferent channels is approximately 12. In the retina of the monkey and cat, the functions of about half of these channels are well-explored. In the rabbit, the fraction is about 30%; the retinas of the mouse and rat, despite their manifest advantages for genetic studies, remain largely unstudied.

It thus may be useful to return, armed with better techniques, to the unfinished business of the 1970s [38]: the task is to finish specifying the functions of the signals transmitted from retina to brain — to identify the missing visual codes — and to identify their targets in the central visual system.

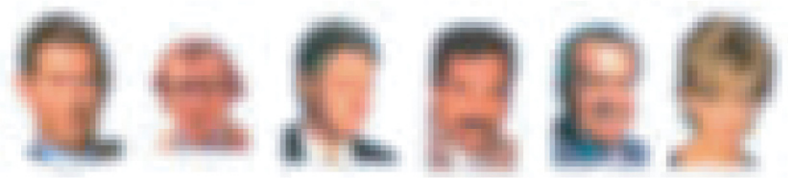

Figure 4. Vision in the absence of spatial detail.

Viewers who are familiar with them will recognize these images, despite the loss of high spatial frequencies. The most distinctive feature of the primate retina is the preponderance of small, highly packed retinal ganglion cells named parvocellular cells. In the absence of high-acuity signals from parvocellular cells, vision is 'blurry' but much useful information remains. Left to right: Prince Charles, Woody Allen, Bill Clinton, Saddam Hussain, Richard Nixon, Princess Diana. (Reproduced with permission from [18].)

Step II: Abandon stimulus ideologies

Why, after more than a half century of work, have physiological descriptions of visual coding lagged so far behind anatomical knowledge, and what can be done to improve matters? Leaving aside the problem of electrode selectivity, a major issue is to choose a strategy for testing the visual tuning of cells.

To learn how cortical (or retinal) neurons are used in vision — their tuning for characteristics of the visual world — turns out to be much more difficult than the field's pioneers imagined. The classic technique was to listen to the cell's amplified spikes while probing a test field with hand-held stimuli; a rapid and effective method, but one that suffers from subjectivity and lack of reproducibility. Simple grating stimuli and linear systems analysis are extremely effective for standard cells [38,39] but, as illustrated above, deal poorly with non-standard cells in cortical afferent pathways and with the essential nonlinearities of cortical neurons. Interesting new attempts to define principled stimulus sets are underway [40], but a consensus is not yet at hand.

An alternative is based on the strategy of reverse correlation [41–43], where a stimulus of the experimenter's choice is presented many times and the responding spike train is used to trigger backward averaging. In this way, the experimenter can build up a representation of the average stimulus that preceded the spike train event. (The event is often a single spike, but it can be any arbitrary pattern of spikes that the experimenter chooses.) The great advantage of this technique is that it does not presuppose any particular tuning of the cell to the test stimulus. For both theoretical and analytical reasons, the test stimulus is commonly chosen to be a 'random' one: a flickering checkerboard or some other form of visual noise. This strategy is elegant in conception, but largely restricted to analysis of standard receptive fields, because non-standard cells (by definition) are tuned to highly non-random features of the possible visual input.

Another alternative takes a more radical approach. The strategy is to reverse correlate the response of the cell to images taken from natural scenes and presented on a video monitor [27,44]. The idea here is that the investigator is asking the cell to describe its own stimulus preferences. The feasibility of this approach has been demonstrated; but an open question is how natural one should consider a two-dimensional image to be, how this method will handle response non-linearities and contextual effects, and how to analyze and display the results in an intuitively accessible manner.

A more general theory of vision?

Reverse correlating the natural world may be viewed as empiricism taken to its extreme. In the opposite methodological corner, what do theoreticians have to offer? We respectfully suggest that theoretical studies might profitably reach beyond the currently popular style, in which the major outcome is a re-statement of experimental results in formal terms. Despite a quarter century's effort, much of this work has proved disappointingly fragile; indeed, the fruits of much labor have simply withered in the face of new experimental facts or shifting fashions of modeling. Although precise and compact statements of experimental results are essential, such statements have rarely led toward a greater synthesis, and the quest for mathematical tractability can impose invidious constraints upon the conduct of experiments. A concrete example was given earlier: if one's experimental apparatus is restricted to the presentation of drifting gratings, the suppressed-by-contrast cell appears only as an 'outlier', about which the investigator can say nothing else.

How, then, could theoreticians contribute? We are experimentalists and ask the question with humility, but we would like to encourage our theoretically inclined colleagues to grapple squarely with computationally inconvenient aspects of real nervous systems. For example, experimental physiologists know all too well that sensory systems are only linear when the experimenter forces them to be so [27,38,45]. The broad reach of theory is needed to deal with facts like this; to make real sense of the relative virtues of redundant and sparse coding in sensory systems; and to continue to build bridges between integrative studies of vertebrate and non-vertebrate vision [46,47].

Our question is whether it would be worthwhile, for these problems of large-system neuroscience, to reemphasize modeling that originates from conceptual first principles [46,48–50]. We have stressed here the florid variety of codes used in the afferent visual pathway of mammals. And yet, the multiplicity of neuronal responses are all designed to serve a single biological computation,

the efficient neural representation of radiant energy that we lump together as vision. This is, in the last analysis, a single task, and the question — the one encountered when we compare the visual systems of men, monkeys and mice — is what we mean by 'seeing'. How should this task be conceptualized? Analogy can be made to studies of human language. Just as mammalian neurons use a variety of different encodings of the visual scene, so do natural languages manifest a huge variety of sounds and linguistic forms. In a way analogous to the study of linguistic deep structure [51–54], and perceptual-cognitive universals [55], order could perhaps be brought to the language of vision by the inspired use of theory.

Acknowledgements

We received helpful suggestions from U. Grünert, C. Tailby, and W.R. Taylor. Supported in part by a Senior Investigator Award to R.H.M. from Research to Prevent Blindness, and by Australian National Health and Medical Research Council grant 253621 to P.R.M.

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